REMARKS

The present application is directed to a therapeutic agent and a method for treatment of mastitis in cattle. Claims 1, 3-5 and 11 were pending. Applicants cancelled Claims 5 and 11, amended Claims 1 and 3-4, and added new Claims 12-16. No new matter has been added. Claim 3 is amended to correct a typographical error. Upon entry of the amendments, Claims 1, 3-4 and 12-16 will be pending.

New Claims

Applicants added new Claims 12-16. Support for the new claims is found throughout the specification and original claims, for example, in the original Claims 1 and 3, and on page 11, lines 18-21 and page 13, top, and lines 7-8 of the specification. Applicants respectfully solicit consideration and allowance of the new claims.

Rejections under 35 U.S.C. §102(b)

Segal et al.

The Examiner rejects Claims 1 and 11 under 35 U.S.C. §102(b) as anticipated by U.S. Patent Serial No. 4,678,772 to Segal *et al.* (hereinafter *Segal et al.*). *Segal et al.* teaches a composition for treatment of oral diseases consisting of glycyrrhizin, sodium fluoride and a phosphoric acid in an aqueous medium. The Examiner asserts that the combination of sodium phosphate and phosphoric acid amounts to a buffer.

Applicants cancelled Claim 11, thereby rendering its rejection moot. Applicants amended Claim 1 to specify the amount of the effective ingredients (glycyrrhizin or pharmaceutically acceptable salts thereof) in the claimed therapeutic agent. Support for the amendment is found, for example, in the specification on page 11, lines 18-21, and page 13, top, and lines 7-8. Applicants respectfully assert that the amendment overcomes the rejection of Claim 1.

Segal et al. teaches a composition for treatment of oral diseases consisting of glycyrrhizin, sodium fluoride and a phosphoric acid in an aqueous medium, which the Examiner asserts to be a pharmaceutically acceptable carrier. Upon amendment, Claim 1 recites glycyrrhizin or pharmaceutically acceptable salts thereof as effective ingredients in an amount adjusted to administer from approximately 400 to approximately 800 mg per mamma, and a pharmaceutically acceptable carrier. Applicants wish to maintain the term "a pharmaceutically acceptable carrier" in Claim 1 and assert that reciting the term in Claims 1 and 3-4 does not preclude their novelty over *Segal et al.*, which fails to teach the amounts of the effective ingredients recited in Claim 1 or a method of treating mastitis. Applicants respectfully assert that *Segal et al.* fails to anticipate the embodiments of applicants' invention claimed in currently amended Claim 1, as well as new Claims 12-13.

Moreover, *Segal et al.* fails to suggest or provide motivation to derive the compositions recited in Claims 1 and 12-13 and fails to render these compositions obvious. Also, *Segal et al.* teaches a method of treatment of <u>oral</u> diseases by directly administering a composition comprising glycyrrhizin to the affected part, but fails to teach, suggest, or provide motivation to derive applicants' method of treatment of mastitis by administering glycyrrhizin. Applicants respectfully assert that *Segal et al* fails to teach, suggest, or provide motivation to derive the applicants' claimed invention and fails to render it obvious.

Elsewhere in the Office Action, the Examiner also cited a publication by Shibata *et al.*, asserting that it teaches a method of treatment of mastitis by administering herbal extracts. Shibata *et al.* extracts possess adverse cytotoxic effects and cannot be used for the applicants' method of treatment of mastitis. Therefore, applicants respectfully assert that combining the teaching of *Segal et al.* with that of Shibata *et al.* results in an inoperable invention, and the combination of the two references fails to teach, suggest, or provide motivation to derive the applicants' claimed invention and fails to render it obvious.

In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claim 1 over *Segal et al.* and favorable consideration and allowance of new Claims 12-13.

Shibata et al.

The Examiner rejects Claims 3-5 under 35 U.S.C. §102(b) as anticipated by Japanese Patent Application No. JP 1-172332 to Shibata *et al.* (hereinafter *Shibata et al.*). The Examiner asserts that *Shibata et al.* anticipates applicants' method of Claims 3-5 because *Shibata et al.* teaches treatment of mastitis by administering plant extracts that contain glycyrrhizin. Applicants cancelled Claim 5, thereby rendering its rejection moot. Applicants respectfully traverse the rejection of Claims 3-4.

According to MPEP 2144.04 VI, "[p]ure materials are novel vis-à-vis less pure or impure materials because there is a difference between pure and impure materials." *Shibata et al.* teaches administering plant extracts, which are mixtures of compounds. Claim 3 recites glycyrrhizin (a "pure material") or pharmaceutically acceptable salts thereof. Therefore, there is a difference between the material used in *Shibata et al.* and in the applicants' method and the applicants' method is novel over *Shibata et al.* for at least this reason.

The Examiner also asserts that, although *Shibata et al.* teaches additional ingredients present in the plant extracts, the additional ingredients do not materially affect the treatment of mastitis. Applicants respectfully disagree. In *Shibata et al.*, the antibacterial components of the plant extracts are effective ingredients for treating staphylococcal mastitis. In contrast, the applicants' method employs glycyrrhizin or its salts as effective ingredients. Glycyrrhizin is not an antibacterial compound. Therefore, according to *Shibata et al.*, the additional ingredients in the plant extracts materially affect the treatment of mastitis.

Specifically, *Shibata et al.* teaches treating staphylococcal bovine mastitis by administering several herbal medicine extracts, including an extract of *G. glabra,* also known

as "kanzo." *G. glabra* contains glycyrrhizin and other compounds, but *Shibata et al.* fails teach isolated or purified glycyrrhizin. *Shibata et al.* also fails to mention uses of glycyrrhizin and fails to designate glycyrrhizin as the *G. glabra* extract ingredient effective for treating mastitis. Therefore, *Shibata et al.* fails to anticipate a method of treating mastitis by administering glycyrrhizin or its salts.

In fact, *Shibata et al.* teaches away from using glycyrrhizin or its salts for treating mastitis. *Shibata et al.* teaches prevention and treatment of bovine mastitis caused by bovine staphylococci (see, for example, p. 3 lines 21-25), comprising administering herbal compositions. *Shibata et al.* teaches several herbal compositions for this purpose: kanzo, huang-lian, ougon, kouboku, tianjin, zhi-mo, chouji, kujin, keihi, biwayou, hops, youbaihi, enmeiso, gobaishi, sanshuyu, shakuyaku, jin ying, chiyu or maou. From this group, *Shibata et al.* fails to select kanzo as particularly effective in treating staphylococcal bovine mastitis, but teaches that kanzo is a relaxant, anticonvulsant and expectorant in humans (see p. 3, line 34-35).

Shibata et al. teaches *in vitro* and *in vivo* antibacterial action of the above herbal compositions against the bacterium *Staphylococcus aureus* (see p. 6, lines 8-13) and correlates the compositions' antibacterial properties with their efficacy in the treatment of staphylococcal mastitis. *Shibata et al.* teaches testing of antibacterial properties of the herbal compositions (see p. 8, Table 1, and Example 1), showing that the antibacterial properties of at least five herbal compositions (youbaihi, zhi-mo, enmeiso, tianjin, and gobaishi) are stronger than those of kanzo. *Shibata et al.* also teaches a preventive effect of the above herbal compositions against staphylococcal mastitis (see Examples 2 to 19, pp. 9-10, Table 2), disclosing that the preventive properties of the same five herbal compositions (youbahi, zhi-mo, enmeiso, tianjin, and gobaishi) are stronger than those of kanzo. *Shibata et al.* teaches that the compositions' antibacterial properties against *S. aureus* make them effective in treatment and prevention of the bovine mastitis caused by *S. aureus*. Therefore,

according to the teachings of *Shibata et al.*, the antibacterial properties of the tested herbal compositions correlate with their preventive properties against staphylococcal mastitis.

Based on the teachings of *Shibata et al.*, one of ordinary skill in the art would know that the antibacterial compounds in the compositions are effective ingredients in the treatment of staphylococcal mastitis. But glycyrrhizin is not an antibacterial compound. It is not known to have antibacterial properties *in vivo* (see, for example, Kai *et al.* (2003), *Am. J. Vet. Res.*, 64:1213-1220, p. 1216, lines 3-9). The applicants' *in vitro* experiments showed that the concentrations of glycyrrhizin used in the applicants' method of treating mastitis had no antibacterial properties. Therefore, according to the *Shibata et al.* method, glycyrrhizin is not the active ingredient of kanzo extract.

Other, antibacterial ingredients of kanzo (*G. glabra* or Xinjian licorice) are known (see, for example, Okada *et al.* (1989), *Chem. Pharm. Bull.*, 37:2528-2530, p. 2528 Table 1, Page 2529, right column lines 30-33). *Shibata et al.* also teaches that kanzo includes antibacterial compounds. Particularly, licochalcone A and glabridin in the kanzo extracts have strong antibacterial properties and are effective against *S. aureus*.

Thus, *Shibata et al.* fails to teach the role of glycyrrhizin in the treatment of cattle mastitis, but identifies the role of other, antibacterial, ingredients of *G. glabra* in the treatment of bovine staphylococcal mastitis. Glycyrrhizin is not an antibacterial ingredient. Therefore, *Shibata et al.* fails to anticipate the applicants' method for at least this reason.

Also, in the applicants' method, the therapeutic agent is administered to the cattle mamma. To facilitate prosecution, applicants amended Claim 4 to specify "direct injection using a cannula." Support for the amendment is found in the specification, for example, on p. 8, line 12, and on page 12, lines 11-12 and 25. *Shibata et al.* fails to teach administering its plant extracts to the cattle mamma, and, in fact, the kanzo extracts in *Shibata et al.* are unsuitable for such purpose, because they contain glabridin, cytotoxic to both tumor and healthy mammalian cells (see, for example, Fukai *et al.* (2000) *Anticancer*

Res., 20:2525-2536, and *Okada et al,* which teaches 9.1% content of glabridin in the extracts on p. 2529, right column, lines 31-35). Thus, the applicants' method cannot be practiced with the kanzo extracts taught in *Shibata et al.* Therefore, *Shibata et al.* fails to anticipate the applicants' claimed method.

In summary, *Shibata et al.* teaches a method of treatment of mastitis by administering herbal extracts, including an extract of kanzo, which comprises antibacterial compounds and glycyrrhizin. *Shibata et al.* fails to teach, suggest, or provide motivation to derive a method of treatment of mastitis by administering glycyrrhizin. In fact, *Shibata et al.* teaches away from treating mastitis by glycyrrhizin by asserting that the plant extracts' active ingredients are antibacterial compounds, whereas glycyrrhizin has no antibacterial properties. Additionally, *Shibata et al.* teaches oral, intramuscular, intraperitoneal, transdermal and intravenous routes administration (see, for example, Page 7 lines 15 to 17, in *Shibata et al.*), but fails to teach or suggest directly administering the plant extracts to the cattle mamma. Furthermore, the extracts used in *Shibata et al.* possess adverse cytotoxic effects and cannot be administered directly to the cattle mamma. Thus, *Shibata et al.* fails to teach, suggest or provide motivation to derive the applicants' claimed invention and fails to anticipate it or render it obvious, alone or in combination with *Segal et al.*, also cited by the Examiner.

In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claim 3-4 over *Shibata et al.*

CONCLUSION

This First Amendment and Response to the Non-Final Office Action is fully responsive. Applicants respectfully assert that the claims are now in condition for allowance and request that the application be passed to issuance. Applicants respectfully request that the Examiner contact the undersigned agent if any questions arise concerning this Amendment and Response.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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